

CASE REPORT

A case of gingival cancer with pulmonary metastases that developed complete atrioventricular block and ventricular fibrillation as a result of myocardial metastases

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Introduction

The incidence of primary heart tumors is very low; they are detected in only 0.1% of all autopsies. Metastatic heart tumors are approximately 20 times more common than primary heart tumors [1]. Metastatic heart tumors arise from a number of different primary tumors such as lung, breast, and hematological malignancies [2]. More than 90% of changes in the heart are asymptomatic; therefore, they remain undetected because the heart is rarely investigated if no symptoms are present [3]. A few cases of sudden death caused by life-threatening arrhythmia derived from myocardial metastasis have been reported in the literature [4]. However, myocardial metastasis from gingival cancer is a very rare occurrence. To date, there have been no reports concerning the stabilization of circulation dynamics by mounting an implantable cardioverter defibrillator (ICD) for life-threatening arrhythmia derived from myocardial metastasis.

Key Clinical Message

We present a rare case of gingival cancer with pulmonary metastases that developed life-threatening complete atrioventricular block and ventricular fibrillation as a result of myocardial metastases. This case suggests that implantable cardioverter defibrillators significantly improve the quality of life in these patients and maintain their performance status.

Keywords

Complete atrioventricular block, gingival cancer, implantable cardioverter defibrillator, lung cancer, myocardial metastasis.

Case Report

A 53-year-old woman found bleeding originating from her left lower gum in 2013. She presented to a dentist and was diagnosed with gingival cancer. A left segmental mandibulotomy and reconstructive surgery with plates was performed in 2014. At the time of the surgery, there were no abnormal findings on computed tomography (CT) and positron emission tomography/CT (PET/CT). A surgical tissue specimen of the gingival cancer showed squamous cell carcinoma (Fig. 1). S-1 monotherapy was therefore administered as postoperative chemotherapy but was discontinued 6 months later because of extreme nausea. Over the next 6 months, the patient complained of cough and neck pain and developed swelling in the left cheek. Chest X-ray and CT revealed a tumor in the right lower lung, which was suggestive of lung cancer. A trans-bronchial lung biopsy was performed via bronchoscopic examination, which revealed squamous cell carcinoma. Although the previously resected gingival tumor was

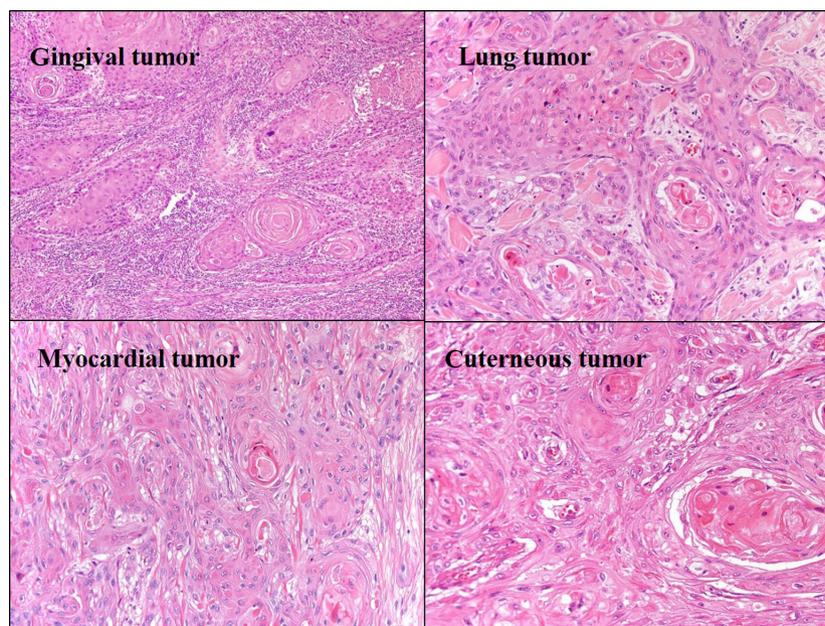


Figure 1. Hematoxylin and eosin staining of pathological tissue harvested from the original resected gingival tumor. The right lower lung, myocardial, and cutaneous tumors in the left submandibular region all showed well-differentiated squamous carcinoma.

proven to be squamous cell carcinoma, it was difficult to differentiate the origin of the primary cancer (Fig. 1). The swelling in the left cheek was thought to represent a recurrence of the gingival tumor, and cutaneous nodules were found in the left submandibular region. The patient was then referred to our hospital for ongoing treatment. Upon physical examination, the patient's body temperature was 36.9°C, pulse rate was 46 beats per min, and systolic blood pressure was 154 mmHg. Oxygen saturation was 94% on room air. Respiratory sounds were reduced in the right lower chest, and she had a clear sensorium. Swelling of the left cheek was clearly evident, and a cutaneous tumor was found in the left submandibular region. Laboratory examinations of her blood revealed no abnormal elevation of tumor markers related to lung cancer (Table 1). An electrocardiogram (ECG) performed upon admission showed complete atrioventricular block, which had not been previously apparent (Fig. 2). Echocardiography revealed a nodule in the atrial septum, which was indicative of myocardial metastasis (Fig. 3). PET/CT further revealed an accumulation of 18F-fluorodeoxyglucose in the atrial septum and left ventricle, a tumor in the left cheek, and a tumor in the right lower lobe and cervical vertebra (Fig. 4). Clinically, these results suggested that the tumor in the left cheek and the cutaneous tumor in the left submandibular region represented a recurrence of gingival cancer because these tumors were located close to the principal gingival cancer, which had been previously resected. The principal differential diagnosis of the tumor

in the right lower lobe was either metastasis from the original gingival cancer or primary lung cancer. Swelling of the mediastinal lymph nodes, cavity formation in the tumor, and the absence of multiple lung metastases suggested a diagnosis of primary lung cancer, although we could not completely rule out gingival cancer at this stage. As a hypothetical diagnosis, the patient was diagnosed with squamous cell lung cancer [clinical T2aN2M1b (OSS) stage IV]. At this point, we did not perform a biopsy of the tumor in the left cheek or the cutaneous nodule in the left submandibular region.

The patient subsequently developed ventricular fibrillation (Fig. 2) and fainted in the hospital 7 days after admission. She was rescued by resuscitation, and an ICD was mounted in her chest to prevent life-threatening arrhythmia 3 days after ventricular fibrillation. Her general condition was defined as performance status 2. The anticancer drug nab-paclitaxel in combination with carboplatin was administered to prevent the recurrence of the gingival and lung tumors 7 days after ICD mounting. However, although the status of the gingival and lung tumor remained stable, the heart tumor progressed after the first cycle of chemotherapy (Fig. 3). The patient's general condition deteriorated, and she died 4 weeks after the anticancer drug was administered. Upon autopsy, specimens of the cutaneous nodule in her left submandibular region and the tumor in the right lower lobe revealed well-differentiated squamous carcinoma. Immunostaining of these two structures was closely

Table 1. Laboratory data upon hospital admission.

Blood		
WBC		5490/ μ L
RBC		369 \times 10 ⁴ / μ L
Hb		10.7 g/dL
Plt		28.3 \times 10 ⁴ / μ L
AST		15 U/L
ALT		12 U/L
LDH		159 U/L
BUN		7 U/L
Cr		0.43 mg/dL
TP		5.8 g/dL
Alb		3.1 g/dL
T-Bil		0.5 mg/dL
D-Bil		0.1 mg/dL
Na		140 mEq/L
K		3.2 mEq/L
Cl		106 mEq/L
Ca		9.8 mg/dL
Glu		156 mg/dL
CRP		0.5 mg/dL
CEA		1.6 ng/mL
CYFRA		2.8 ng/mL
SCC		2.7 ng/mL
ProGRP		37.8 pg/mL
KL-6		116.0 U/ml
SP-D		122.2 ng/mL
BNP		250.6 pg/mL
FDP-DD		1.8 μ g/mL
β -D glucan		<6.0 pg/mL
Aspergillus antigen		(-)
Index		0.23
Candida antigen		(-)
Urine		
Uric blood		(-)
Urinary sugar		(-)
Albuminuria		(-)
Leukocyturia		(-)

matched, and the two tumor types were thus likely to be derived from a common primary cancer (Table 2). Dysplastic cells were not detected in the bronchoepithelial cells harvested from the tumor in the right lower lobe. Myocardial metastases in the atrial septum and left ventricle were confirmed to be well-differentiated squamous carcinoma (Fig. 1) and had infiltrated the atrioventricular node (Fig. 5). This was considered to be the cause of the life-threatening arrhythmia. Other areas of metastases were confirmed in the lungs, liver, and kidneys. Ultimately, the cause of her death was cancer, mainly due to the progression of myocardial metastases.

Discussion

In this case, the patient underwent a left segmental mandibulotomy for gingival cancer. At the time of the

surgery, a chest CT and PET/CT did not reveal any abnormal findings. After a period of approximately 12 months, the patient developed swelling in her left cheek, a cutaneous nodule in the left submandibular region, and a tumor in the right lower lobe. These events emerged almost simultaneously. It was difficult to differentiate whether the primary cancer responsible for these lesions was a recurrence of the gingival or lung cancer because the tissue diagnosis and immunostaining from all tissue types showed well-differentiated squamous carcinoma. We finally determined that all of the lesions were due to the recurrence of gingival cancer rather than primary lung cancer because of the history of gingival cancer, and no dysplastic cells were detected in bronchoepithelial cells harvested from the tumor in the right lower lobe. These findings were consistent with well-differentiated squamous carcinoma. The frequency of tumor metastasis to the heart is reported to be 7.1% in cancer patients and 2.3% of all autopsies [5], whereas primary cardiac tumors are reported in 0.1% of all autopsies. The frequency of tumor metastasis to the heart is approximately 20 times that of primary cardiac tumors. Reports have cited several sources for the primary lesion in cases involving tumor metastasis to the heart, including lung cancer, breast cancer, malignant melanoma, malignant lymphoma, and leukemia [6]. The frequency of lung metastasis in cases that had metastasized from head and neck cancer was reported to be 83.4% and 86.7%, respectively, and all of those patients died within a year. The median survival period was reported to be 4.3 months [7]. Although multidisciplinary treatment was performed in these cases, curative therapies have not yet been established for head and neck cancer.

Autopsies have shown that the frequency of tumor metastasis to the heart from primary oral cancer is approximately 7% [8]. In other reports, it was shown that oral cancer metastasized to the node in the myocardium, and metastasis was found in the heart cavity in a form resembling vegetation [8, 9]. On the other hand, the frequency of tumors metastasizing to the heart in lung cancer is much higher, approximately 18–36% [10]. In 67 cases of myocardial metastasis or metastasis to the pericardium in lung cancer, 59 cases exhibited metastasis in only the pericardium, whereas one case exhibited metastasis in the myocardium alone [11]. Independent metastasis to the myocardium in lung cancer appears to be an infrequent event. Little is known regarding the mechanisms underlying metastasis to the heart, although one report showed that 18 of 23 cases of myocardial metastasis or metastasis to the pericardium in lung cancer were caused by retrograde lymphatic metastasis [12]. In our patient, myocardial metastasis in both the atrial septum and left ventricle was confirmed to represent differentiated

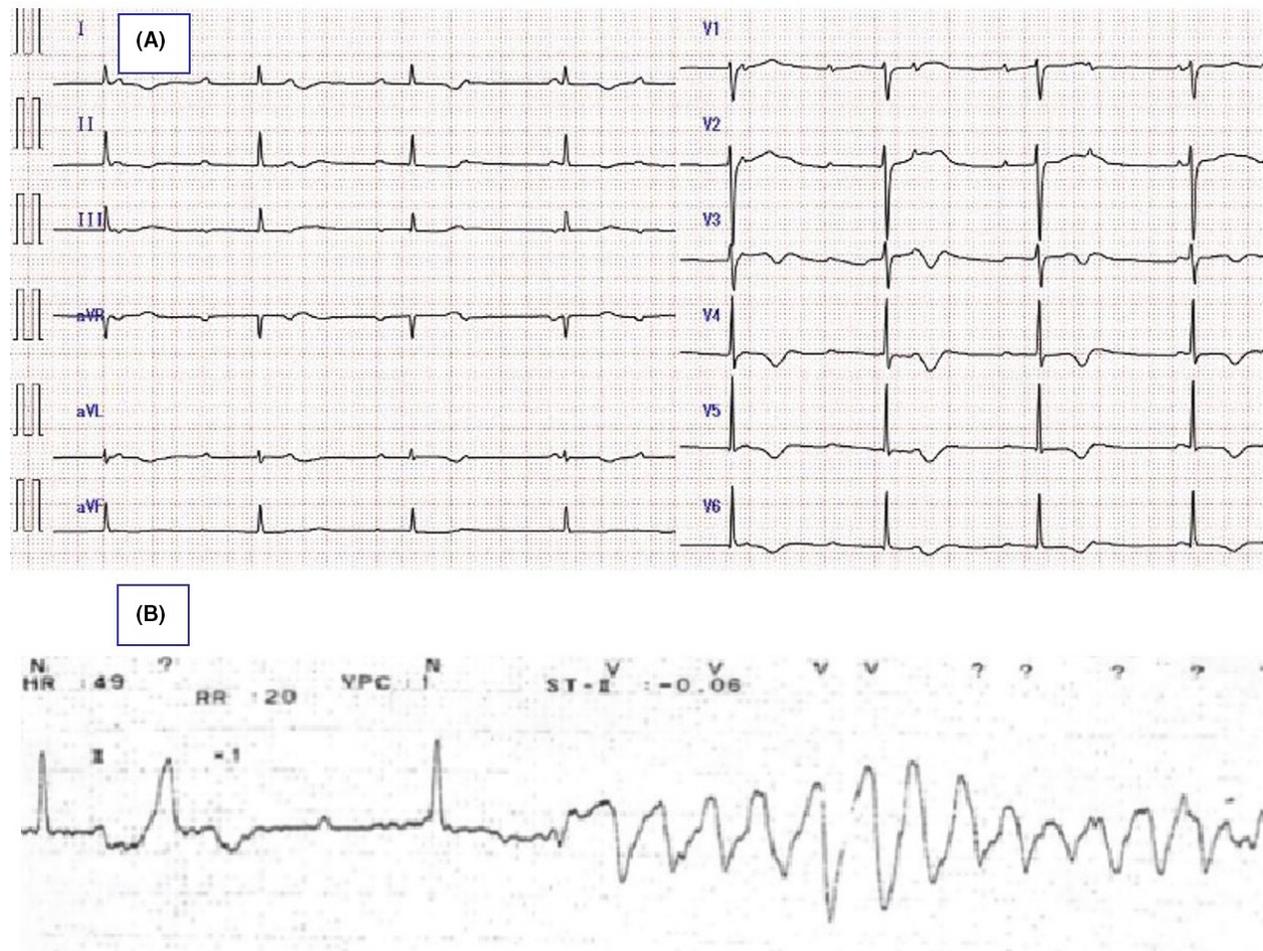


Figure 2. Electrocardiogram (ECG) upon admission showed a complete atrioventricular block that had not been apparent earlier (A). The patient subsequently developed ventricular fibrillation in the hospital (B).

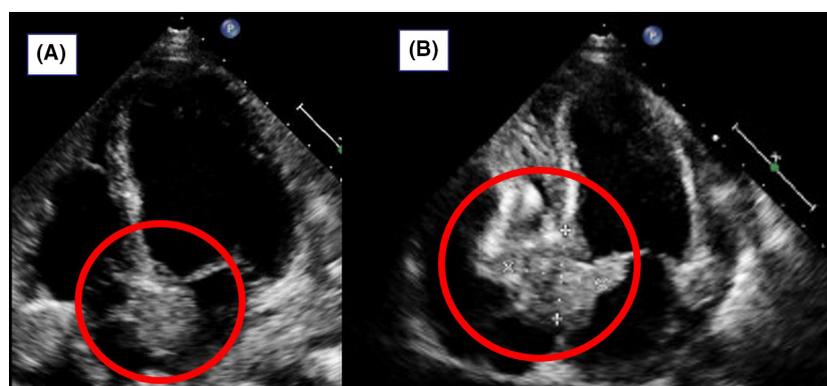


Figure 3. Echocardiograph showing a nodule in the atrial septum, which was suspicious of myocardial metastasis (A).The heart tumor increased in size following the first cycle of chemotherapy (B).

squamous carcinoma. Lymph ducts surrounding the myocardial metastases were not invaded by cancer, which suggested that myocardial metastases had developed by

hematogenous metastasis. Cardiac effusion was detected in our patient by both CT and echocardiography. Because infiltration to the pericardium could not be confirmed on

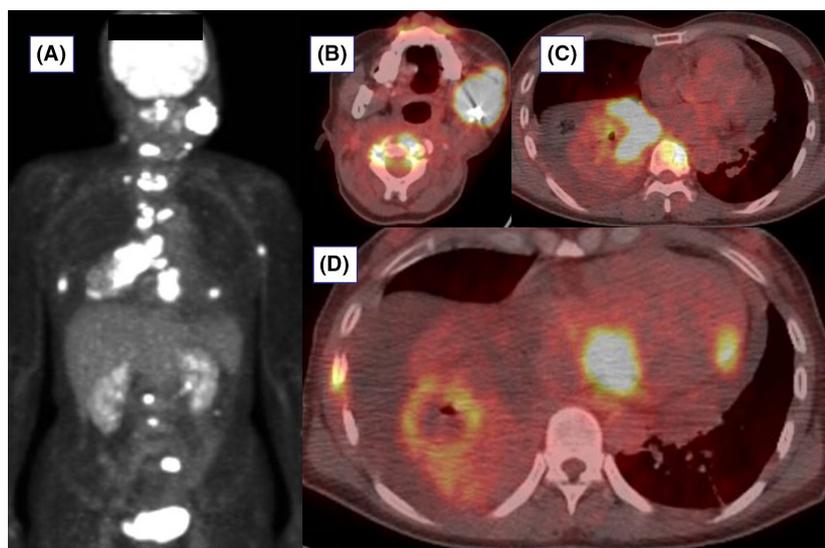


Figure 4. Scout image of positron emission tomography/computed tomography (A) showing the accumulation of 18F-fluorodeoxyglucose in a tumor in the left cheek (B), a tumor in the right lower lobe (C), and myocardial tumor (D).

Table 2. Immunostaining of biopsies taken from the cutaneous tumor in the left submandibular region and right lower lung. These appeared identical.

	CK5/6	p40	p63	CK7	CK20	CEA	p53
Cutaneous tumor in the left submandibular region	+	+	+	-	-	+	+
Right lower lung	+	+	+	-	-	+	+

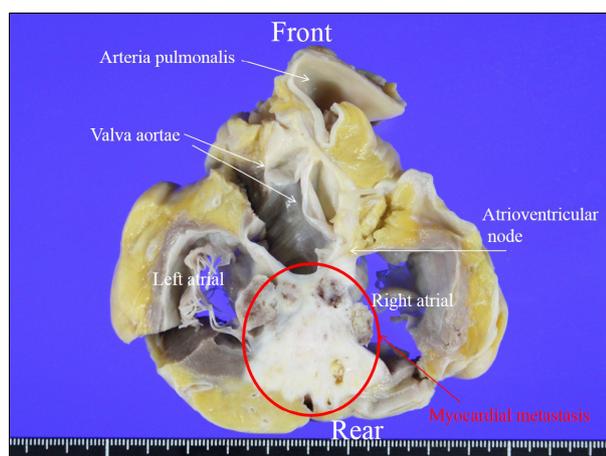


Figure 5. Myocardial metastases infiltrating into the atrioventricular node.

autopsy, it was clear that carcinomatous pericarditis did not exist. Therefore, our case was not consistent with hematogenous metastasis from gingival cancer to the

myocardium. We therefore diagnosed this case as a recurrence of gingival cancer with metastases to the cheek, skin, lung, and myocardium.

With respect to the diagnosis of myocardial metastasis, more than 90% of myocardial metastasis is known to be asymptomatic and remains undiscovered prior to death. Myocardial metastasis was suspected because of various factors, including an ST-T wave change in the ECG and the appearance of a myocardial lead obstacle such as atrial fibrillation, atrial flutter, premature ventricular contraction, complete atrioventricular block, and acute cardiac infarction [13, 14]. It has been suggested that in such cases, confirming wall movement decline by echocardiography, evaluating changes in the brightness of the myocardium, and assessing increases in the myocardial thickness of the wall are required [15]. It has also been reported that heart magnetic resonance imaging (MRI) can detect a tumor in the heart in a more sensitive manner than echocardiography [16]. The use of qualitative assessments of the myocardium in lung cancer by PET/CT has also been reported [17]. When our patient was admitted to the hospital, her ECG showed complete atrioventricular block, an observation that had not been made previously. Furthermore, a nodule in the heart cavity, which had been confirmed by echocardiography, was strongly indicative of myocardial metastases. In addition, the accumulation of 18F-fluorodeoxyglucose was confirmed in the heart by PET/CT. We therefore made a clinical diagnosis of myocardial metastases. Because ventricular fibrillation occurred after admission, an ICD was surgically implanted. Therefore, image assessment of myocardial metastasis by MRI could not be performed.

Implantable cardioverter defibrillator insertion is a treatment that clearly involves numerous risks, including tumor embolus, and imaging becomes impossible as tumors develop. However, we elected to use an ICD implant because we expected better circulation dynamics and an improvement in general condition. At least temporarily, life-threatening arrhythmia was prevented; thus, the patient avoided a sudden death. The introduction of chemotherapy also became a possibility. Autopsy confirmed the infiltration of myocardial metastases around the atrioventricular node. This was considered to be the causative factor underlying the main heart problem. Generally, it is difficult for cancer to infiltrate the myocardium because of the dense arrangement of blood vessels and the smooth muscle elastic fibers that make up the tissue. It is also considered that the implantation of cancer cells is obstructed by the persistently high internal pressure in the blood vessels [18]. In addition, it was recently discovered that the hormone atrial natriuretic peptide (ANP), which is released from the atrium, acts upon the vascular endothelium and is thought to restrain the metastasis of cancer [19]. Therefore, one possible reason for such a low incidence of heart and myocardium metastasis is high ANP levels. Because cardiac tamponade obstructs the expansion of the atria and ventricles, secretions of ANP and brain natriuretic peptide were reported to be restrained under these conditions [20]. As in the case of lung cancer, there have been many reports of myocardial metastasis with cardiac effusion. It has been suggested that the restraint of ANP secretion by diastolic obstacles represent a background factor in myocardial metastasis. In our case, although vital signs were stable, cardiac effusion was confirmed, thus creating an environment in which the secretion of ANP was restrained. In our patient, autopsy could not confirm infiltration of the pericardium by cancer. It was therefore difficult to consider carcinomatous pericarditis as a diagnosis. Rather, this was regarded as cardiac effusion related to hypoalbuminemia. With respect to the site of metastasis for myocardial metastasis, there have been several case reports stating that life-threatening arrhythmia can be derived from myocardial metastasis near the atrial septum [14, 21]. Differences in ANP distribution have been reported in different regions of the heart. For example, one report claimed that there was more ANP secretion in the right atrium than in the left atrium, more ANP secretion in the epicardium than in the endocardium, and ANP levels were low in the atrial septum [22]. If the function of ANP is to restrain the metastasis of cancer, it follows that cancer will readily be able to develop metastasis at the atrial septum because ANP levels are low at this location. Further research on ANP is necessary to elucidate whether this hypothesis is true. Chemotherapy can be used to treat myocardial metastasis, and it has been reported that local radiation treatment can be used

effectively in the treatment of this condition [23]. However, it has been reported that radiation treatment in the presence of an ICD implant could cause permanent damage to semiconductors in the ICD [24]. Local radiation therapy for the myocardial metastases was not performed for the reasons given earlier.

Myocardial metastasis often occurs in the final stages of cancer, and the only remaining option for patients is palliative care. In our case, ICD implantation was conducted, and the patient's general condition improved to the point where we could introduce chemotherapy. We believe that there are arguments both for and against the insertion of ICD in patients with myocardial metastasis of cancer. In our case, because complete atrioventricular block was confirmed with an ECG, insertion of the ICD was adopted from the view point of cardiovascular disease. Insertion of the ICD itself involves risk; if complete atrioventricular block is not confirmed on ECG, insertion of an ICD may not be essential. In that case, the patient should be followed carefully and assessed frequently to detect any abnormalities on ECG.

Although it was difficult to ascertain whether insertion of an ICD could lead to a good prognosis, it prevented sudden death, which has often been reported in patients with myocardial metastasis of cancer. We believe insertion of an ICD would make a significant improvement to the quality of life in these patients and maintain their performance status.

In conclusion, we report a rare case of myocardial metastases with life-threatening arrhythmia originating from gingival cancer. We believe that an ICD implantation could be selected as one means of palliative care. Unfortunately, the efficacy of chemotherapy in our patient was not sufficient. Further research should be conducted to elucidate mechanisms of myocardial metastasis and to develop an effective therapeutic approach.

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Conflict of Interest

The authors declare that they have no conflict of interests.

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